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US-PAT-NO: 6355425
DOCUMENT-IDENTIFIER: US 6355425 B1

TITLE: Mutations associated with iron disorders

DATE-ISSUED: March 12, 2002

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US-CL-CURRENT: 435/6; 536/22.1

CLAIMS:

What is claimed is:

1. A method of diagnosing an iron disorder or a genetic susceptibility to developing said disorder in a mammal, comprising determining the presence of a mutation in exon 2 of an HFE nucleic acid in a biological sample from said mammal, wherein said mutation is not a C.fwdarw.G substitution at nucleotide 187 of SEQ ID NO:1 and wherein the presence of said mutation is indicative of said disorder or a genetic susceptibility to developing said disorder.

2. The method of claim 1, wherein said disorder is hemochromatosis.

3. The method of claim 1, wherein said nucleic acid is a DNA molecule.

4. The method of claim 1, wherein said nucleic acid is a RNA molecule.

5. The method of claim 1, wherein said mutation is a missense mutation at nucleotide 314 of SEQ ID NO:1.

6. The method of claim 5, wherein said mutation is 314C.

7. The method of claim 6, wherein said mutation results in expression of mutant HFE gene product I105T.

8. The method of claim 1, wherein said mutation is at nucleotide 277 of SEQ ID NO:1.

9. The method of claim 8, wherein said mutation is 277C.

10. The method of claim 9, wherein said mutation results in expression of mutant HFE gene product G93R.

11. The method of claim 1, wherein said mutation is at nucleotide 193 of SEQ ID NO:1.

12. The method of claim 11, wherein said mutation is 193T.

13. The method of claim 12, wherein said mutation results in expression of mutant HFE gene product S65C.

14. The method of claim 1, wherein said biological sample is selected from the group consisting of whole blood, cord blood, serum, saliva, plasma, effusions, ascites, urine, stool, buccal tissue, liver tissue, kidney tissue, cerebrospinal fluid, skin, hair and tears.

15. The method of claim 14, wherein said biological sample is whole blood.

16. The method of claim 14, wherein said biological sample is saliva.

17. The method of claim 14, wherein said biological sample is hair.

18. The method of claim 1, wherein said mammal is a human.

19. The method of claim 1, further comprising amplifying said nucleic acid using a first oligonucleotide primer which is 5' to exon 2 and a second oligonucleotide primer is 3' to exon 2.

20. The method of claim 1, further comprising amplifying said nucleic acid using a first oligonucleotide primer which is 5' to nucleotide 314 of SEQ ID NO:1 and a second oligonucleotide primer which is 3' to nucleotide 314 of SEQ ID NO:1.

21. The method of claim 1, further comprising amplifying said nucleic acid using a first oligonucleotide primer which is 5' to nucleotide 277 of SEQ ID NO:1 and a second oligonucleotide primer which is 3' to nucleotide 277 of SEQ ID NO:1.

22. The method of claim 1, further comprising amplifying said nucleic acid using a first oligonucleotide primer which is 5' to nucleotide 193 of SEQ ID NO:1 and a second oligonucleotide primer which is 3' to nucleotide 193 of SEQ ID NO:1.

23. The method of claim 20, 21, or 22, wherein said first oligonucleotide primer has a nucleotide sequence of SEQ ID NO:3 and said second oligonucleotide primer has a nucleotide sequence of SEQ ID NO:4.

24. The method of claim 20, 21, or 22, wherein said first oligonucleotide primer has a nucleotide sequence of SEQ ID NO:15 and said second oligonucleotide primer has a nucleotide sequence of SEQ ID NO:16.

25. A method of diagnosing an iron disorder or a genetic susceptibility to developing said disorder in a mammal, comprising determining the presence or absence of a mutation in an intron of HFE genomic DNA in a biological sample from said mammal, wherein the presence of said mutation is

indicative of said disorder or a genetic susceptibility to developing said disorder.

26. The method of claim 25, wherein said mutation is in intron 4.

27. The method of claim 26, wherein said mutation is at nucleotide 6884 of SEQ ID NO:27.

28. The method of claim 27, wherein said mutation is 6884C.

29. The method of claim 25, wherein said mutation is in intron 5.

30. The method of claim 29, wherein said mutation is at nucleotide 7055 of SEQ ID NO:27.

31. The method of claim 30, wherein said mutation is 7055G.

32. The method of claim 25, further comprising amplifying said nucleic acid using a first oligonucleotide primer which is 5' to intron 4 and a second oligonucleotide primer which is 3' to intron 4.

33. The method of claim 25, further comprising amplifying said nucleic acid using a first oligonucleotide primer which is 5' to intron 5 and a second oligonucleotide primer which is 3' to intron 5.

34. A method of diagnosing an iron disorder or a genetic susceptibility to developing said disorder in a mammal, comprising determining the presence of a mutation in a HFE gene product in a biological sample from said mammal, wherein said mutation results in a decrease in an intramolecular salt bridge formation in said HFE gene product but is not amino acid substitution H63D, and wherein the presence of said mutation is indicative of said disorder or a genetic susceptibility to developing said disorder.

35. The method of claim 34, wherein said disorder is hemochromatosis.

36. The method of claim 34, wherein said mutation is between amino acids 23-113, inclusive, of SEQ ID NO:2.

37. The method of claim 34, wherein said mutation is between amino acids 58-68, inclusive, of SEQ ID NO:2.

38. The method of claim 34, wherein said mutation is between amino acids 60-65, inclusive, of SEQ ID NO:2.

39. The method of claim 34, wherein said mutation is amino acid substitution S65C.

40. The method of claim 34, wherein said mutation is between amino acids 90-100, inclusive, of SEQ ID NO:2.

41. The method of claim 34, wherein said mutation is between amino acids 92-97, inclusive, of SEQ ID NO:2.

42. The method of claim 34, wherein said mutation is amino acid substitution G93R.

43. The method of claim 34, wherein said mutation is at amino acid 95 of SEQ ID NO:2.

44. The method of claim 34, wherein said mutation is detected by immunoassay.

45. A method of diagnosing an iron disorder or a genetic susceptibility to developing said disorder in a mammal, comprising determining the presence of a mutation in a HFE gene product in a biological sample from said mammal, said mutation being located in the .alpha.1 helix of said HFE gene product, wherein the presence of said mutation is indicative of said disorder or a genetic susceptibility to developing said disorder.

46. The method of claim 45, wherein said mutation is between amino acids 80-108, inclusive, of SEQ ID NO:2.

47. The method of claim 45, wherein said mutation is I105T.

48. The method of claim 45, wherein said mutation is G93R.

49. An isolated nucleic acid molecule encoding an HFE polypeptide comprising amino acid substitution I105T or the complement thereof.

50. An isolated nucleic acid molecule encoding an HFE polypeptide comprising amino acid substitution G93R or the complement thereof.

51. An isolated nucleic acid molecule encoding an HFE polypeptide comprising amino acid substitution S65C or the complement thereof.

52. A kit for detecting a nucleotide polymorphism associated with an iron disorder or a genetic susceptibility to developing said disorder in a mammal comprising the nucleic acid molecule of claims 49, 50, or 51.

53. A kit for the detection of the presence of a mutation in exon 2 of an HFE nucleic acid comprising a first oligonucleotide primer which is 5' to exon 2 and a second oligonucleotide primer is 3' to exon 2.